AREA OF EMPHASIS:

Natural History and Epidemiology

SCIENTIFIC ISSUES

In the United States and other industrialized countries, AIDS diagnoses and deaths peaked in the 1980s and then showed a steep decline from the mid-1990s through 2001. These improvements were mostly attributable to the widespread use of new and effective treatment regimens, particularly antiretroviral (ARV) drugs. In recent years, however, while the death rate among persons with AIDS has continued to decline, the rate of decline in AIDS diagnoses has slowed and since 2001 has shown a slight increase each year.

The composition of the epidemic in the United States, and in many other industrialized countries, has also changed. New HIV infections now occur more frequently in racial and ethnic minorities, groups with high-risk sexual behaviors, injecting drug users, and adolescents. The use of potent antiretroviral therapy (ART) has favorably influenced the progression of HIV disease, extending the time between HIV infection and development of AIDS. A more complex pathology, however, is being uncovered as HIV-infected people live longer and develop age-related comorbidities. In addition, while very effective in improving the health of HIV-infected people, ART has been associated with a wide variety of undesired effects in many organ systems. Epidemiologic research has been instrumental in identifying and describing such effects, disentangling effects related to treatment from those related to HIV disease itself. Since the beginning of the HIV epidemic, NIH-supported epidemiologic research has also played a key role in elucidating the interplay of virus, host, and environment. However, the changing face of the epidemic, with new groups and populations being affected, requires that rigorous epidemiologic studies be conducted in those different settings.

Worldwide, studies have shown a global spread of a heterogeneous epidemic, mostly fueled by heterosexual transmission and, in some geographic areas, augmented by injecting drug use. The rollout of ART initiatives is slowly gathering steam. Thus, ART is now becoming a more frequent backdrop in places where research on HIV/AIDS is being conducted. NIH-supported research on HIV/AIDS can play a major role in providing the scientific basis for the implementation of treatment and prevention programs. Well-designed epidemiological studies are a key component of such research, as they help to characterize local epidemics; the respective effects of viral, host, and environmental factors on HIV transmission and disease progression; and the measurable effects of ART. Additionally, the value of traditional research in the epidemiology of HIV/AIDS will increase when complemented by operational or translational research, a discipline that will define the optimal process of treatment and care to achieve the best outcomes.

PRIORITY FOR FUTURE RESEARCH:

- **Sponsor domestic and international epidemiologic investigations into the interactions between HIV genetic variability, host genetics, and other factors that influence disease morbidity and mortality, with special emphasis on different routes of transmission, chronic and infectious comorbidities and malignancies, and long-term use of antiretroviral therapies.**

Since the beginning of the HIV/AIDS epidemic, numerous studies have revealed features in the virus and the host that are associated with the variable likelihood of virus transmission or the variable rate of HIV disease progression once a person is infected. Virus characteristics such as the virus amount (or viral load) and the use by the virus of some, but not other, cellular coreceptors have been commonly associated with more frequent HIV transmission and/or more rapid disease progression. Among the viral characteristics that have been found to influence transmission dynamics and the rate of appearance of disease, the virus genomic variability has been investigated in depth, as it is the quintessential feature of HIV. This feature is particularly important in the context of ART, as it influences decisions about ART strategies at the community level and the choice of specific ART regimens for individual patients. The investigation of these viral characteristics continues to require studies in epidemiologically well-characterized populations, particularly as more and different treatment regimens are being tested worldwide including, more recently, in many developing countries. In a setting of rapid and continued evolution of the virus, the monitoring of such viral features as recombination and development of resistance to ARV drugs is critically important to curtail transmission, optimize the effectiveness of ARV treatment regimens, and save therapeutic options for future use.

To date, less research has been conducted about the effects of genetic variation in the human host on HIV disease progression and transmission of HIV. These

studies require careful long-term followup of study participants, but have potentially important implications for interventions (i.e., by guiding decisions about accelerating or delaying antiretroviral treatment or about the expected response of different ethnic groups to AIDS vaccines).

Studies of certain HIV transmission modalities, such as mother-to-child transmission (MTCT), have resulted in the use of prevention measures that have led to a dramatically lower level of *in utero* and peripartum HIV transmission in the industrialized world. Similar prevention measures, based on various ARV drug regimens, are now more widely used in developing countries as well. Further research, however, is necessary to find an adequate answer to the problem of HIV transmission postpartum. Through breastfeeding, a very common practice in developing countries, HIV can be transmitted from an infected mother to a nursing baby in a sizable proportion of cases.

Regardless of the route of HIV transmission—perinatal, sexual, or through contaminated needles—research efforts must continue to identify the critical biological and behavioral cofactors that influence morbidity and mortality due to HIV, as the identification of modifiable factors constitutes a necessary prerequisite to the development of successful interventions.

Rigorous NIH-sponsored epidemiological studies are needed for the detailed measurements of morbidity and mortality rates in the presence of comorbid conditions. These include a broad spectrum of conditions, tuberculosis (TB) and hepatitis being among the most common worldwide, which can both be difficult to manage and negatively affect the outcome of ART. Correct epidemiological methods will also allow for the measurements of undesired effects of long-term ARV treatment. Such undesired effects, which may differ according to gender and ethnicity, require in-depth study and linkage to specific ARV regimens ascertained and confirmed in different populations.

PRIORITY FOR FUTURE RESEARCH:

- **In order to increase the value of different sources of epidemiologic information on HIV/AIDS, develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies of populations experiencing emerging and ongoing HIV epidemics, with particular emphasis on:**
  - **Assessing the short- and long-term effects of preventive and therapeutic interventions at the individual, family, and community levels;**
  - **Establishing integrated databases that allow analyses of large datasets to address new or unresolved scientific questions; and**

- **Generating new hypotheses regarding the transmission and pathogenesis of HIV infection.**

Traditionally, the generation and dissemination of quality data has been the basis for performing sound epidemiologic analyses and reaching conclusions that are both valid and applicable to multiple settings and populations. The acquisition of reliable data can be achieved through multiple research instruments, including data collection approaches that minimize errors and the acquisition, storage, and maintenance of biologic specimens. The availability of specimen repositories from long-term studies is a critical resource for basic science investigations, the development of new biologic assays, and the exploration of drug-related toxic effects or adverse events in genetically varied populations. In addition, the development and maintenance of a domestic and international research infrastructure is necessary for the study of biological and behavioral aspects of HIV/AIDS in new or previously understudied populations. The NIH will continue to emphasize the importance of cohort studies to investigate the rate of HIV disease progression, the causes of death, and the impact of therapies on the changing spectrum of HIV disease. Study populations that are carefully characterized in terms of their demographics, ethnic origin, genetic makeup, and presence or absence of risk factors for HIV/AIDS will provide the basis for a variety of studies, ranging from observational studies that describe the history of disease to experimental studies that compare different intervention modes. The former describe a large number of biologic events and the biologic parameters that change around those events. They can thus show patterns of infection and disease under various circumstances and also lead to the generation of new scientific hypotheses. The latter allow for the testing of treatments, preventive or therapeutic, and the determination of their safety and efficacy. Observational studies also constitute a critical complement to clinical trials to assess the long-term effects of preventive and therapeutic interventions at the individual, family, and community levels.

The NIH will further develop the use of information technology tools to address the unique and evolving research questions that cannot be answered by single cohorts. The use of research instruments for information collection and analysis, such as relational databases, allows for the conduct of large studies, domestically and internationally, with previously unattainable levels of precision and overall quality. In addition, such databases allow for comparisons of cohorts and populations worldwide that are investigated using the same standardized research approach. NIH-funded databases will foster the creation of new collaborative studies, particularly in settings where standardization of research methods is difficult, such as in resource-limited settings. The assembly of new, representative cohorts, specimen repositories, and integrated databases in developing countries will be important to study key cofactors (e.g., infectious, nutritional, host genetic-related) that modify HIV disease and to assess their role in the response of individuals and populations to HIV drug treatments or vaccines. Enabling technologies, including bioinformatics, will be

key NIH instruments in increasing the quality of NIH-supported research and the widespread dissemination of its findings.

PRIORITY FOR FUTURE RESEARCH:

- **Implement epidemiologic and simulation studies among HIV-infected individuals and appropriate controls to inform, monitor, and evaluate intervention strategies, including initiation of treatment programs, in domestic and international settings.**

The rate at which the HIV/AIDS epidemic progresses in previously identified populations or penetrates in new populations needs to be constantly monitored to improve the quality of epidemic surveillance, a key aspect in infectious disease epidemiology. Population-based studies supported by the NIH are critically important to describe the epidemic patterns, identify risk factors that may accelerate or slow their progress, and provide a rational basis for preventive and therapeutic interventions. The NIH will continue to support and refine epidemiologic investigations and simulation studies in numerous and diverse populations in the United States and worldwide. The study of large numbers and various types of populations is necessary to identify new foci of epidemic spread and also to determine the effects of interventions in different populations and specific circumstances. For example, it is important to measure the impact of interventions on the risk-taking behavior of groups for whom those interventions are devised, since studies have documented that such behaviors may increase as a result of a false sense of security.

The knowledge acquired through this type of research can inform the design of intervention strategies, ensure that they are evidence-based, and make them applicable to many diverse settings. It can also help to prioritize interventions in developing countries, where resources for HIV/AIDS prevention and control are severely limited in the face of competing health needs.

Furthermore, as more intervention approaches are developed and implemented, epidemiologic studies will have to incorporate cost-effectiveness parameters and analyses. This is of particular importance in resource-limited countries.

PRIORITY FOR FUTURE RESEARCH:

- **Continue improving key measures to diagnose and monitor HIV/AIDS in diverse settings by encouraging development of and evaluating late-generation laboratory assays. These include accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; and markers of toxicity and comorbidity for use in domestic and international settings.**

As for other infectious conditions, the role of laboratory tests cannot be overemphasized for the diagnosis, prevention, management, and, ultimately, control of HIV/AIDS. There is a direct relationship between the availability and correct use of laboratory tests and the ability to monitor HIV-related infection and disease. Such tests are a necessary complement to clinical observation and experience for the diagnosis and management of individuals. In addition, accurate and reproducible laboratory assays are the basis to rapidly acquire knowledge of the HIV epidemic in different populations and geographic areas.

A variety of assays has been developed and is now being routinely used in the industrialized world. Besides the more widely known serologic tests, other more recently developed laboratory tests include assays that measure the immune status of HIV-infected individuals (e.g., CD4 lymphocytes and other cellular components of immune defenses), viral replication, and other viral characteristics (e.g., viral RNA, DNA, nucleotide sequence, coreceptor utilization). The development of sensitive, specific, and reproducible laboratory assays is a key research endeavor that the NIH will continue to foster. Although the design and development of such assays constitutes an interdisciplinary effort involving various aspects of basic science, their testing and evaluation in humans requires the careful application of epidemiologic principles to correctly ascertain both assay-related and population-related properties. Both sets of properties are essential to ascertain the assays' performance characteristics and robustness under different conditions. In developing countries, simple and rapid assays are necessary to define the epidemiologic features of emerging or evolving epidemics.

Assays are also needed to monitor HIV treatment toxicities, as the expanding therapeutic armamentarium increases the likelihood of undesired treatment effects. As treatment for HIV becomes more widely available in resource-limited countries, affordable assays are urgently needed for clinical diagnosis and monitoring and for use in hard-to-reach areas. There is a particular need to develop and evaluate assays that are self-contained and have long shelf life under unfavorable environmental conditions. Assay development and evaluation should also determine or parallel the determination of normative values for clinical and laboratory settings in resource-limited countries.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations to guide prevention and treatment strategies.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES:

- Utilize existing cohorts, including incidence cohorts, to further assess HIV transmission and acquisition.
- Conduct studies on the molecular epidemiology and the effects on HIV transmission of infection with different HIV subtypes, routes and modes of transmission, ARV-resistant viruses, multiple subtypes, and recombinant viruses.
- Evaluate sexual and blood-borne HIV transmission and acquisition in relation to the following:
  - Viral factors such as viral quantity (measures of viral RNA and other quantification methods) in various body compartments (e.g., blood, saliva, and mucosal compartments), viral diversity (intrapatient diversity), and HIV genotype, including subtypes, recombinants, resistance mutants, and dual virus infections;
  - Host factors such as age, sex, hormonal status, strength and breadth of immune response, mental health, patterns of alcohol and drug use, and host genetic factors;
  - Modifiable host factors such as diet and nutritional status; drug, alcohol, and tobacco use; use of exogenous hormones; use of traditional medicines, herbal medicines, and supplements; other infections, including oral infections; other causes of mucosal pathology, including sexually transmitted diseases (STDs); and circadian rhythm;
  - Biological, behavioral, cultural, and environmental determinants of susceptibility to HIV acquisition and progression among women and girls;
  - Persistent exposure to HIV (i.e., in HIV-discordant couples);
  - Use of microbicides and barrier devices;
  - Social, cultural, behavioral, and ecologic factors, including such demographic characteristics as socioeconomic status, race, ethnicity, gender, culture, religion, community, and geographic location (e.g., rural, urban, suburban);

  - Sexual activity, choice of partner, duration of partnership, abstinence, marital fidelity, control of STDs, hygienic practices, contraception choices, and cultural practices such as use of traditional vaginal preparations, female genital mutilation, and male circumcision; and
  - Extent to which environmental and other macro-level factors such as war, migration, refugee status, homelessness, drug trafficking patterns, political will, and disasters influence vulnerability, risk behaviors, acquisition, and access to care in developed and developing countries.

- Conduct studies (including community-based studies) to understand and quantify the effect on HIV transmission and HIV incidence of widespread use of ART by eligible individuals.
- Conduct community-based studies that assess the impact of community mobilization on prevention and treatment success.
- Study and quantify the impact on HIV transmission of adherence to ART and related factors such as therapy and regimen characteristics, drug characteristics, and symptom management.
- Study the impact of widespread ART availability and resulting viral load suppression on patterns of risk behavior.
- Conduct epidemiological studies on the role of coinfection and comorbidity with other microbial agents in modifying the acquisition and course of HIV infection and in predicting the evolution of particular HIV/AIDS epidemics. Research should focus on hepatitis GB virus C (GBV-C), *M. tuberculosis* (TB), *Plasmodium sp.* (malaria), human papillomavirus (HPV), hepatitis C (HCV), herpesvirus type 8 (HHV-8/KSHV), or other sexually or nonsexually transmitted conditions within existing programs and settings (e.g., MTCT).
- Evaluate the impact on HIV transmission and disease progression of hormonal contraceptives and replacement therapies, composition of such therapies, pharmacokinetics, and duration of action of repository-form contraceptives.
- Employ epidemiological techniques to evaluate and quantify the impact of different intervention strategies on HIV transmission and prevention.
- Examine the effects of vaccine trials on HIV transmission characteristics, including the effects on the alteration of transmission by vaccine-induced immunity. Examine the clinical course and markers of infectiousness among vaccine trial participants with breakthrough HIV infection to determine the vaccine's effect on viral load, rates of progression, and on population HIV incidence.

- Conduct studies on medication-assisted substance abuse treatment modalities and access to service (e.g., methadone maintenance, buprenorphine/naloxone, naltrexone, antabuse, acamprosate, and stimulant abuse therapy), alone or in combination with mental health and/or behavioral interventions as HIV prevention interventions, and examine their effects on HIV disease progression, adherence to ART, and acceptance of care and treatment.
- Identify effective individual, network, and community-level interventions and determine the coverage needed to decrease HIV incidence in developing and developed countries.
- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including treatment of the mother, infant feeding modalities, physiology of lactation, long-term effects of perinatal interventions, maternal and infant genetic variation, and kinetics of viral resistance.
    - Assess the impact of breastfeeding practices on MTCT of HIV and on the health of children and mothers.
    - Define how the physiology of lactation affects HIV transmission.
    - Assess the impact of maternal ARV regimens of different potency and duration on MTCT of HIV and on the short- and long-term health of women and their children who are eligible for ART.
    - Study the safety and effectiveness of low-cost, sustainable approaches to prevention of MTCT of HIV, including exclusive breastfeeding in the first months of life with rapid weaning.
    - Assess the impact of perinatal treatment and prophylaxis regimens on emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis.
    - Assess the impact of maternal ART on transmission during pregnancy and lactation.
    - Assess the impact of maternal and infant adherence to ARV regimens on the effectiveness of MTCT, the risk of subsequent ARV resistance, and the effectiveness of ART in mothers and their children.
    - Assess the impact of perinatal treatment and prophylaxis regimens on communitywide HIV resistance to ARVs.
    - Determine the impact of ARV resistance on perinatal transmission and pediatric infection.

- Assess the impact of MTCT programs on public health measures, including maternal, paternal, and infant morbidity/mortality rates; overall life expectancy; disability-adjusted life years; and child developmental milestones.

OBJECTIVE - B:

Use epidemiological research in domestic and international settings to identify the influence of therapeutics and other biological (e.g., host genetics, coinfections, HIV subtypes) and behavioral (e.g., access, adherence) factors on HIV progression, as shown by virologic, immunologic, and clinical outcomes.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES:

Strategies Related to Disease Progression and Response to ART

- Investigate the contribution of innate host characteristics to viral measures, immune function, disease progression, and mechanisms for these effects (including host genetic factors and their modulators, sex, race, and age).
- Examine how chronic inflammatory processes (and such mediators as inflammatory cytokines) that result from HIV and other concurrent infections, stress, or depression modify immune function, disease outcomes and survival, and response to ART.
- Assess the effect of treatment for HIV and comorbid conditions on the incidence and pathogenesis of cancer.
- Characterize the changing spectrum of clinical outcomes (morbidity and mortality), including causes of death associated with evolving therapeutic strategies, domestically and internationally.
- Elucidate the pathogenic mechanisms that influence residual HIV replication in ART recipients.
- Investigate the effect on disease progression of viral factors, including viral subtype, fitness, and innate and acquired genotypic and phenotypic resistance to ARVs.
- Conduct epidemiological and modeling research to improve estimates of per contact risk of HIV transmission over the course of the disease process, from acute infection to onset of advanced HIV disease.
- Determine the global patterns of viral resistance (innate and acquired) to ART and how these patterns could influence the long-term effectiveness of these therapies.
- Define the prevalence and incidence of HIV-associated nephropathy and its influence on mortality and response to ART in developing countries.
- Identify, characterize, and determine the frequency, changing manifestations, and effects of HIV-related respiratory disease on morbidity, mortality, and

HIV disease progression (e.g., immune reconstitution syndromes affecting the lungs [including sarcoidosis], HIV-related pulmonary hypertension, accelerated emphysema, and coinfections) in domestic and international populations, including both untreated patients and those receiving ART.

- Develop new cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease and evaluate interventions, especially in minority populations and developing countries.
- Characterize the epidemiology of those recently HIV infected, including host and viral genetic characteristics, and continue to characterize the epidemiology of HIV/AIDS infection among those who have minimal exposure to ART, those who have virologic and/or immunologic responses to these therapies, and those who have failed these therapies.
- Conduct studies on the pharmacogenomic determinants of the distribution and fate of ARV drug distribution throughout body compartments and of the treatment response in racially and ethnically diverse populations.

Strategies Related to Complications of Therapy

- Identify the effects of HIV and ART on disease outcomes, including (1) other HIV-associated diseases, including central and peripheral nervous system conditions, oral and mucosal lesions; (2) other infectious diseases; and (3) metabolic complications (e.g., lipoatrophy, hyperlipidemia, diabetes mellitus, osteopenia/osteoporosis, and steatosis) and long-term disease outcomes, including malignancies and associated oncogenic infections and cardiovascular disease.

Strategies Related to Comorbidities

- Evaluate the rate of HIV disease progression in populations with variable comorbidities such as poor nutrition, opportunistic infections (OIs), and other non-AIDS-defining infections.
- Intensify research on the spectrum of HIV-associated malignant diseases that may develop in HIV-infected persons, who are expected to live longer with subclinical immune deficiency.
- Establish normative data for lymphocyte subsets, total white blood cell count, and total lymphocyte count in developing countries, and determine the influence of common comorbidities, especially malaria, TB, and helminth infection.
- Investigate TB-HIV interactions, including the effects of dual infection on the infectiousness and progression of both TB and HIV and the effect of various treatment strategies on disease control.

- Evaluate the impact of treatment of alcohol abuse, drug abuse, and mental health disorders on the effectiveness of ART, including in the context of specific forms of drug use.
- Assess the effect of HIV on other infections (e.g., hepatitis B [HBV], HCV, GBV-C, other blood-borne infections, cytomegalovirus [CMV], JC virus, HPV, KSHV, TB, and malaria and other parasitic diseases) and the effect of these infections and their treatment on HIV outcomes.
- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections (e.g., multidrug-resistant TB, sulfa-resistant malaria, antibiotic-resistant pneumococcus, cotrimoxazole-resistant *Pneumocystis carinii* pneumonia [PCP], and lamivudine-resistant HBV) in HIV-infected populations.
- Encourage epidemiological studies of dual infection with HIV and HCV, and incorporate research on HCV infection within existing programs of research on HIV/AIDS.
- Assess the effect of other non-ART interventions (e.g., statin use, cancer treatment) on disease outcomes and survival.

Strategies Related to MTCT and Pediatric Infection

- Study HIV-infected children and adolescents to determine factors related to impaired growth and neurodevelopment, cognitive development, impact of other childhood infectious diseases, and safety and efficacy of immunizations, and how these may be affected by medical and behavioral interventions.
- Evaluate the long-term complications of maternal and infant ART among exposed, HIV-uninfected children.
- Examine the effect of the health status of HIV-infected mothers and of ART during pregnancy and lactation on survival of their children, both HIV-infected and -uninfected.
- Investigate the long-term outcome of complications in HIV-infected pediatric populations as these children reach adolescence and adulthood.

Strategies Related to Aging

- Investigate the relationship between HIV infection and other comorbidities (HIV-associated and non-HIV-associated) that increase with aging, such as obesity, hypertension, and emphysema, on disease outcomes (e.g., liver disease, cardiovascular disease, and renal disease) and survival.

- Study the incidence and determinants of physical and cognitive decline in aging HIV-infected individuals, and the effect of frailty and functional impairment on HIV, ARV use, and self-care behaviors.
- Characterize the changing spectrum of clinical outcomes, including cancers, in the treated, chronically infected, aging, HIV-infected populations living with prolonged immune suppression.
- Study the effect of HIV and ART (e.g., response to treatment, adverse effects) in aging populations with coexisting morbidities and polypharmacy.

Strategies Related to Adherence, Access, and Quality of Life

- Study determinants of adherence to ART and adverse events of such therapies in domestic and international settings, and in all age groups.
- Investigate how different patterns of access, adherence, and exposure to ART in treatment-experienced and treatment-inexperienced populations contribute to ARV resistance and disease progression.
- Identify the individual, provider, and infrastructure factors associated with initiating, continuing, adhering to, and discontinuing ART, and evaluate the impact of these factors on therapeutic outcomes.
- Evaluate the effects of modifiable host characteristics, specifically behavioral characteristics including adherence, substance use, sexual behavior, and cultural practices, on viral measures, immune function, disease progression, and mechanisms for these effects.
- Elucidate the effects of HIV infection on sleep disturbances, including prevalence, possible immunological and endocrine mechanisms, associations with HIV outcomes, possible changes with ART, and influence on quality of life and cardiovascular health.

OBJECTIVE - C:

Develop and evaluate methods and resources for HIV/AIDS epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory, sampling, and statistical methods with information systems; and better integrate research findings into clinical practice and regional, national, and international policy.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES:

- Evaluate and promote the use of study designs that incorporate appropriate ethical, cultural, and policy context for HIV/AIDS studies in diverse domestic and international populations.
- Ensure that the population composition of domestic epidemiological studies reflects the shifts in the populations most at risk for and affected by HIV/AIDS, including older Americans.
- For studies in both domestic and international settings, improve approaches for recruitment and retention of underrepresented populations, including minorities, children, adolescents, women, drug and alcohol abusers, incarcerated populations, and persons living with mental illness.
- Support training and mentorship of medical and health professionals in developing countries in the areas of research ethics, study design, informatics, data management and analysis, and linking research trials to clinical care, and clinical care to health policy and implementation.

Strategies Related to Natural History/Pathogenesis

- Encourage development of and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, pharmacologic, and genetic assays suitable for large-scale epidemiological research and surveillance in developing nations. Emphasis should be on simple and reliable staging of disease progression for the initiation and monitoring of ART and OI prophylaxis; HIV resistance testing; and noninvasive diagnostic assays for STDs, other OIs including TB, and AIDS-related malignancies.
- Develop new epidemiological designs and statistical methods, including development of informatics tools, to better characterize transmission dynamics and monitor long-term trends in disease progression in the setting of potent ART.
- Develop, maintain, and effectively cultivate ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies. Nested studies that utilize these

resources should be particularly encouraged and developed.

- Use observational data to better characterize the natural history of AIDS-associated conditions in international settings and trends in the epidemiology of these conditions.
- Develop methods for assessing HIV-related quality of life that are feasible and culturally appropriate.
- Develop uniform assessment tools to measure host and environmental characteristics, including substance abuse and mental health, which may impact immediate and long-term HIV-related health outcomes. Assessment tools should be culturally appropriate without the loss of scientific validity.

Strategies Related to Interventions

- Study the various operational strategies that can be employed to "bring to scale" ART programs, including the use of operations research and integrated databases to evaluate treatment effectiveness at the individual, community, and population levels.
- Assess the effectiveness and comparability of clinical versus laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-poor settings.
- Develop appropriate clinical and laboratory definitions of short-term and long-term ARV failure and develop mechanisms for monitoring and assessing drug resistance evolution in HIV-1 variants and subtypes in domestic as well as international settings.
- Evaluate the impact of continued ART after the failure of multiple regimens.
- Study the impact of access to ART and vaccines on risk behaviors and HIV acquisition among at-risk populations.
- Develop, evaluate, and promote new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion, medical treatments, and other iatrogenic exposures in developing countries, including instrument sterilization.
- Assess the impact of different strategies for HIV testing and their linkage to care.
- Develop simulation strategies (modeling) of the impact of interventions on HIV transmission, cofactors of HIV infection, and communitywide morbidity and mortality, including non-HIV-infected individuals (i.e., survival of uninfected infants).

Strategies Related to Policy

- Evaluate the long-term clinical and nonclinical impact and the cost-effectiveness of different strategies for care, including treatment of AIDS-associated conditions (e.g., OIs, anemia) and ART.
- Improve methods for disseminating research, making research results more accessible to all stakeholders, and provide the scientific basis for regional and national standards of care, as well as formal HIV best practice guidelines.
- Develop formal methods to assess the applicability and transportability of guidelines for care of HIV-infected individuals across countries.
- Support HIV policy research, including economic impact studies, necessary for translating epidemiological and clinical studies into policy.

FY 2007 OAR Planning Group for National History and Epidemiology

FY 2007 NATURAL HISTORY AND EPIDEMIOLOGY PLANNING GROUP

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